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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 3 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Memorandum:

SUBJECT: PP#1G3930. Request to Decrease the Temporary Tolerance and to Extend the Experimental Use Permit for the Use of Avermectin B₁ on Apples. 618-EUP-13. (MRID# 430141-01, CBTS#12909. DP Barcode 197373).

FROM: Jerry B. Stokes, Chemist
Chemistry Branch/Tolerance Support
Health Effects Division (7509C)

THRU: Philip V. Errico, Section Head
Tolerance Support Section III
Chemistry Branch/Tolerance Support
Health Effects Division (7509C)

TO: George LaRocca/Linda Arrington, PM-13
Fungicide-Herbicide Branch
Registration Division (7505C)

Jerry B. Stokes
P. V. Errico

Merck Research Laboratories, Merck & Co., Inc., requests an extension and a decrease of a temporary tolerance for the residues of the miticide avermectin B₁ and its delta 8,9 geometric isomer in/on apples (fresh market only) from 0.05 ppm to 0.02 ppm. Abamectin is the accepted ANSI and ISO common names and is defined as a mixture of avermectins containing $\geq 80\%$ avermectin B_{1a} (5-0-demethyl avermectin A_{1a}) and $\leq 20\%$ avermectin B_{1b} (5-0-demethyl-25-de(1-methylpropyl)-25-(1-methylethyl) avermectin A_{1a}). Both of these exist in the 8,9-E configuration and may undergo trans to cis olefin isomerization at the 8 and 9 carbons to produce the corresponding 8,9-Z-avermectin B_{1a} and 8,9-Z-avermectin B_{1b}. Therefore these isomers are also included in the tolerance expression.



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Tolerances for the combined residues of the insecticide avermectin B₁ and its delta-8,9-isomer have been established in 40 CFR §180.449 for tomatoes at 0.01 ppm, citrus, whole fruit at 0.02 ppm, cottonseed at 0.005 ppm, milk at 0.005 ppm, and cattle, meat and meat byproducts at 0.02 ppm (40 CFR §180.449); citrus oil at 0.10 ppm (40 CFR §185.300); and tomato pomace at 0.07 ppm and dried citrus pulp at 0.10 ppm (40 CFR §186.300). Tolerances are pending for use of avermectin on various agricultural commodities including pears, strawberries, celery, lettuce, almonds, almond hulls, and walnuts.

For this EUP, the proposed use is the following:

A single rate of 0.025 lb a.i./A + 1.0 gallon oil/A will be applied twice in a minimum plot size of 4 tree X 4 tree design with the four center trees used for sampling. Plot size may also range up to 5 acres or more. The spray will be delivered in a minimum of 40 gpa for concentrated tests and up to 400 gpa for dilute tests. A total of 225 acres are requested for the tests which are spread over 14 states (state, acres: WA, 50; NY, 50; MI, 20; PA, 20; CA, 20; VA, 10; NC, 10; WV, 10; OR, 10; ID, 5; OH, 5; CO, 5; ME, 5; NJ, 5). The total a.i. (avermectin B₁) for the trials is 11.25 lb. Treated apples will only be harvested for fresh market sales; apples treated in this experimental program will not be processed into food/feed products. The proposed experiment will be run between April 1, 1994 and December 31, 1994. The objectives of the experimental use permit are to determine efficacy, phytotoxicity, and product performance under different application rates.

Comments/Conclusions:

1. The manufacturing process has been adequately discussed in previous tolerance requests. CBTS concludes that impurities are not likely to be a residue problem.
2. The directions for use are adequate.
3. Plant metabolism data were not submitted with this petition. Data were previously submitted for celery, cottonseed, and citrus. The nature of the residue is understood for the purposes of this temporary tolerance. The residue of regulatory concern is avermectin B₁ and its delta 8,9 isomer.
4. Animal metabolism data were not submitted with this petition. Although wet and dry apple pomace are animal feed items, these studies will not be needed for this temporary tolerance because the treated apples will not be processed into food/feed items. In addition, only 225 acres over a 14 state area are proposed in this experimental program.
5. The proposed analytical methodology (Method No. 8000) is the same as submitted for pears. This methodology is acceptable

by CBTS for avermectin B₁ and the delta 8,9 isomer residues in/on apples.

6. No storage stability data are submitted in this petition. The storage stability data submitted for pears will be translated for apples for the purposes of this temporary tolerance only.
- 7a. Adequate residue data are submitted for apples for this EUP only.
- 7b. Data from an apple processing study are submitted in this petition. This study will not be needed for this temporary tolerance because the treated apples in this experimental project will not be processed into food/feed items. In addition, only 225 acres over a 14 state area are proposed in this EUP. However, for a permanent use, feed additive tolerances will be needed.
- 7c. The petitioner must add a label restriction to read: Grazing or harvesting of forage from treated orchards is not permitted.
8. Secondary residues are not expected in meat or milk because the apples treated in this EUP will not be processed. Likewise, no residues are expected in poultry or eggs. However, for a permanent use, meat and milk tolerances may be need revision. Tolerances for poultry and eggs may be needed.
9. There are no Codex limits for abamectin (defined by Codex as the sum of avermectin B_{1a}, avermectin B_{1b}, and the delta 8,9-isomer of avermectin B_{1a}) in apples. There are no Canadian, or Mexican limits established for abamectin and its delta 8,9 isomer. Therefore, no compatibility problems exist.

Recommendations:

Provide a label restriction is added as stated in Conclusion 7c, CBTS can recommend for the extension of the EUP and the decrease of the temporary tolerance for the residues of avermectin B₁ and its delta 8,9 isomer in/on apples at 0.02 ppm.

For a permanent tolerance for apples the petitioner is advised to follow 40 CFR 158 and the Residue Chemistry and Product Chemistry Guidelines. We also advise the petitioner to address the following requirements for a permanent tolerance.

- * Residue data must reflect the proposed use on apples at the maximum rate and the minimum proposed 28 day PHI. An adequate geographical representation of major apple growing areas should be submitted.

- * Residue data for processed apple commodities (juice, wet and dry pomace) must reflect crop treatment at the maximum application rate and the minimum PHI.
- * Storage stability data of avermectin B₁ and its delta-8,9 isomer in/on r.a.c., apples and in apple juice and pomace (wet and dry) must be provided.
- * Validation and recovery data using the proposed analytical methodology must be provided.
- * The petitioner should be prepared to conduct additional plant metabolism studies if the use patterns differ significantly from those proposed for or registered on pears, cotton, citrus, or tomatoes.
- * The petitioner should provide a new goat metabolism study, with 14C-labelled material, at elevated feeding levels if the dietary burden to livestock is increased by the proposed use on apples.
- * Feed additive tolerances for apple pomace, wet and dry, will be needed.

Detailed Considerations

Manufacture and Formulation

Avermectin is produced by a fermentation process using a strain of Streptomyces avermilitis. This process yield 4 homologous pairs of closely related compounds: avermectin A₁, A₂, B₁, and B₂. The avermectins are extracted from the culture broth and purified by recrystallization. Abamectin is the technical grade active ingredient in the proposed 2.0% formulation. Abamectin is the accepted ANSI and ISO common names and is defined as a mixture of avermectins containing $\geq 80\%$ avermectin B_{1a} (5-0-demethyl avermectin A_{1a}) and $\leq 20\%$ avermectin B_{1b} (5-0demethyl-25-de(1-methylpropyl)-25-(1-methylethyl) avermectin A_{1a}). The manufacturing process for technical abamectin and its contents have been discussed previously (PP#4F3065, memo of 9/13/84, V. Frank Boyd; PP#5G3287, memo of 12/10/85, L. Cheng). The TGAI contains ca. 1% of unidentified impurities related to the avermectins. The TOX Branch has stated that the impurities are not of concern (PP#5G3287, memo of 3/12/86, W. Dykstra). CBTS concludes that the impurities are not likely to be a residue problem, and there are no problems with the manufacturing process.

The formulated product is AGRI-MEK 0.15 EC Miticide/Insecticide. One gallon of the emulsifiable concentrate (EC) contains 0.15 lbs abamectin as the active ingredient.

Proposed Use

For control of mites and other damaging insects on apples during mid-to-late season, the above formulation is applied at 10-20 fl. oz./A (0.0125 - 0.025 lb. a.i./A), not to exceed more than 20 oz./A/application or 40 fl. oz./A/season, in a minimum of 40 gallons of water per acre for concentrated sprays and up to 400 gallons of water per acre for dilute sprays. Applications are made with a paraffinic oil in both the dilute and concentrated sprays with no more than 1.0 gallon of paraffinic spray oil per acre in the finished spray. Only ground equipment should be used. The proposed PHI is 28 days. Presently the petitioner has a label restriction that applications are to be made only to fresh market apples. CBTS would like to caution the petitioner that such a label restriction will not be acceptable for a permanent use on apples, since CBTS does not recognize fresh market apples as a separate rac. Note: The petitioner must add a label restriction to read: Grazing or harvesting of forage from treated orchards is not permitted.

Nature of the Residue:

Plants: No new plant metabolism data were submitted in this petition. Data were submitted on celery, cottonseed, and citrus (PP#'s 5G3220, 5G3287, and 8F3649) and have been discussed previously (See memos of: 12/15/89, S. Willett, PP#9F3703; 7/89/87, C. Deyrup; 11/16/88, 2/13/89 and 6/21/89, V. F. Boyd).

For the purpose of establishment of a temporary abamectin tolerance in/on apples, the metabolism data is adequate. The residues of regulatory concern are abamectin and its delta 8,9 isomer.

Animals: No additional animal metabolism data were submitted in this petition. Although apple pomace (wet and dry) is considered animal feed items, the petitioner has stated that the apples will only be marketed as fresh, and will not be processed into food/feed products. In addition, the proposed treatment of 225 acres spread over a 14 state area would be small and would not require additional animal metabolism data to support this EUP or a temporary tolerance.

For a permanent tolerance in/on apples, the petitioner is advised of CBTS's previous comments (See memo of 12/15/89, S. Willett, PP#9F3703) that if registration on additional feed items causes the dietary burden in livestock to increase, a new C14 goat metabolism study may be required.

Analytical Methodology

Analytical methodologies have been previously submitted for citrus, tomato, celery, cottonseed, and pears. In all methods residues of

avermectin and its delta-8,9 isomer are extracted into organic solvents, passed through cleanup procedures, derivatized, and quantified by reverse phase HPLC with fluorimetric detection. A successful validation by the Agency has been completed for Method No. 1009R3 (citrus), and has been submitted to FDA for inclusion in PAM II as Method I. Method No. 6004 (cottonseed) has been submitted to FDA for inclusion in PAM II as a letter method since a method trial was not run by the Agency. The method of choice for avermectin B₁ residues on apples is No. 8000, the same method submitted for pears (PP#9F3787). This method differs from the others in that an initial enzymatic step is necessary before the plant matrix can be adequately extracted for avermectin B₁ residues. A successful validation by the Agency has been completed for Method No. 8000 on pears. CBTS has completed comments on this methods (See memo of 12/16/93, G. Herndon).

Validation data for apples are submitted in this petition. Fortification levels for avermectin B_{1a} and the delta 8,9 isomer (1.9, 4.8, 40, and 79 ppb, and 5.3, 26, and 70 ppb, respectively) and one level for the avermectin B_{1b} (5.9 ppb), recoveries ranged from 79 to 108 % for avermectin, and 97 to 126% for the delta 8,9 isomer using Method No. 8000. The limit of detection is 1 ppb. The limit of quantiation is 2 ppb.

Therefore, for the purposes of this EUP, the analytical methodology will be adequate to support the temporary 0.02 ppm tolerance in/on apples. However, for a permanent use on apples, adequate validation data, in addition to residue data using this methodology for apples must be submitted. Chromatographic charts for standards, field-treated samples, fortified samples, and untreated controls must be submitted.

Although not needed for the proposed EUP, the petitioner has submitted analytical methodology for apple processed fractions. Method No. 92-1 is submitted for the determination of avermectin B₁ and its delta-8,9 isomer in apple processed fractions, i.e., wet and dry pomace, applesauce, raw and clarified juice. This method uses liquid-liquid extraction/homogenization and solid phase extraction cleanup procedures along with fluorescence derivation using 1-methylimidazole/trifluoroacetic acid in acetonitrile. This method is similar to that used for tomatoes. Validation data for these processed items are submitted in this petition. Fortification levels (and recoveries) for avermectin B_{1a}, avermectin B_{1b}, and the delta 8,9 isomer in wet and dry pomace ranged from 2.0 to 100 ppm (69-97%), and 5 and 12 ppm (72-96%), and 5.2 to 100 ppm (52-74%), respectively. Fortification levels (and recoveries) for avermectin B_{1a}, avermectin B_{1b}, and the delta 8,9 isomer in applesauce ranged from 2.1 to 103 ppm (71-83%), and 5 ppm (80-86%), and 5.2, 26, and 100 ppm (69-73%), respectively. Fortification levels (and recoveries) for avermectin B_{1a}, avermectin B_{1b}, and the delta 8,9 isomer in apple juice (raw and clarified) ranged from 2.0 to 62 ppm (55-109%), and 3.1 ppm (87-

106%), and 6.2 to 62 ppm (53-82%), respectively. The limit of detection is 1 ppb. The limit of quantitation is 2 ppb.

Storage stability data have not been submitted for apples, but CBTS will translate the pear storage stability data (PP#9F3787, MRID# 411885-14) to support this EUP for apples. Four set of samples were fortified with avermectin B_{1a} (10.2 or 71.0 ppb), B_{1b} (10.0 ppb), or delta 8,9 isomer (5.3 ppb). Samples were stored frozen and analyzed at 43, 92, 183, and 365 days. Two replicates were run for each fortification (except 3 for 10.2 ppb B_{1a}) with recoveries ranging from 62 to 111%, with averages of 86% for B_{1a}, 89% for B_{1b}, and 93% for delta 8,9 isomer. One sample of B_{1a} gave 0% recovery, but it was questioned if the sample received the initial fortification. A freshly fortified sample (10.2 ppb B_{1a}) run in parallel gave 85% recovery. Control data were adequate.

Apple samples were stored shortly after harvest under freezer conditions (-10 to -20 C). Therefore for the purposes of this EUP only, adequate storage stability data is available to support the proposed experimental use of avermectin on apples. However for a permanent tolerance on apples, adequate storage stability data for abamectin treated apples and any processed products from these abamectin treated apples must be submitted to the Agency.

Residue data

A 0.05 ppm temporary tolerance was established based upon pear residue data submitted in PP#9F3787. The proposed decrease in the tolerance is now supported by apple residue data.

Abamectin residue data has been submitted from 14 states (state, acres: CA, GA, MI, NY, NC, OR, and WA. These states represent approximately 70% of US production. Most of the data reflect 1X (12 trials at 0.024 lb a.i./A, the remaining 2 trials at 0.025 lb a.i./A). Only 2 trials were conducted at a 2X (0.05 lb a.i./A) rate. PHI's ranged from 0 to 45 days. The spray volumes were twice applied, using an airblast orchard sprayer in 12 trials and a handheld sprayer in only 2 trials, ranged from 37 to 400 gpa (5 at 40 gpa, 4 at 75 gpa, 3 at 250-300 gpa, and 2 at 350-400 gpa). At the proposed 28-day PHI, the combined residues of abamectin and its delta 8,9 isomer, ranged from 0.002 to 0.012 ppm at the proposed 1X rate, and from 0.003 to 0.010 ppm at the 2X rate. The 2X rate (0.05 lb a.i./A) is the maximum allowed per season. Chromatographic charts for standards, field-treated samples, fortified samples, or controls were submitted with these reports. Based upon the residue data for apple trials using the proposed 28-day PHI, the proposed 0.02 ppm tolerance would adequately cover any abamectin residues (avermectin B₁ plus in/on treated apples.

Trial No.	Loc.	No of Appl.	Rate, lb a.i./A	Spray Vol., gpa	PHI, days	Total Abamectin Residues, ppb
001-90-5016R	NY	2	0.025	400	28	2.0-3.8
001-90-5018R	MI	2	0.025	300	28	3.7-6.9
001-91-1021R	WA	2	0.024	267-301	28	2.0, 3.0
001-91-1023R	WA	2	0.024, 0.023	75	28	3.0, 3.9
001-91-1024R	MI	2	0.024	79	28	3.0, 3.4
001-91-3000	NY	2	0.024	75	28	4.5-7.9
001-91-6016R	CA	2	0.024	75	28	9.1, 12.2
001-91-6024R	CA	2	0.024	272-278	28	2.0
001-92-0026R	NC	2	0.024	39-41	28	3.0, 3.6
001-92-0027R	GA	2	0.024	40	28	2.0, 3.0
001-92-1014R	OR	2	0.024	37-42	28	2.0
001-92-1018R	WA	2	0.024	40-41	28	2.0, 3.0
001-92-3020R	NY	2	0.024	40	28	3.0, 4.7
001-92-6012R	OR	2	0.024	349-359	28	2.0, 4.3

Method recoveries of fortified samples (2 to 50 ppb avermectin B₁) ranged from 85 to 105%. The petitioner should be advised that a permanent tolerance on apples will require adequate residue data for abamectin in/on treated apples at the maximum rate and the minimum PHI which are representative of the major US apple growing states. Chromatographic charts for treated samples, fortified samples, and controls must be submitted.

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Data from a processing study are submitted in this petition. Samples for the processing were collected from trial 001-92-3000R. Samples were taken at 7 and 28 days following two applications at 0.024 lb a.i./A. The samples were analyzed for abamectin residues.

RAC/Processed Item	Total abamectin residues, ppb	Concentration factors
raw apples	9.45 (7 days) 6.7 (28 days)	
whole unwashed apples	9.1 (7)	
wet pomace	44.3	4.7
dry pomace	154	16.4
raw apple juice	0.5	0.05
clarified apple juice	0.5 (7 days) 0.5 (28 days)	0.05 0.07

Based upon the above data, there appears to be a concentration in apple pomace, both wet and dry. (See Discussion of Meat, milk, poultry, and eggs, this memo, for additional comments.)

Meat, milk, poultry, and eggs

Temporary tolerances are established for avermectin B₁ and its delta 8,9 isomer in cattle meat and meat byproducts (0.02 ppm) and milk (0.005 ppm) with expiration dates of 3/31/93, but RD has extended these tolerances.

A 28-day feeding study (See PP7G3468, Acc#265585) was reviewed previously (See memo of 2/11/87, L. Cheng). Feeding levels of avermectin B₁ were 10, 30, and 100 ppb. The avermectin residues are summarized as follows:

Dose (ppb)	Avermectin B ₁ Residues (ppb)				
	Liver	Muscle	Fat	Kidney	Milk
10	3-4	1-2	2	1-2	<1
30	5-8	2	4-6	2	<1
100	18-20	2	10-14	4-5	<1-4

Apple pomace (wet and dry) is an animal feed item. Dry pomace may comprise upto 50% of the beef cattle diet, upto 25% of dairy cattle

diet, and upto 5% of turkey and broiler diets. Laying hens and swine are not normal fed apple pomace. In this petition, however, the treated apples will not be processed. Thus, apple pomace will not be available for animal feeding. Therefore, there is no reasonable expectation of finite residues in livestock with this experimental use of abamectin on apples.

Again, CBTS would like to caution the petitioner that a label restriction "For fresh market apples only" will not be acceptable for a permanent use on apples, since CBTS does not recognize fresh market apples as a separate rac. Therefore based upon the processing study, 409 tolerances must be proposed for wet and dry apple pomace for the permanant use.

No changes in the tolerances are necessary at this time. However, if a permanent tolerance is established on apples, then the dietary burden of livestock must be reviewed to determine the need for any tolerance increases, if necessary, in meat, meat byproducts, poultry, and milk.

Other considerations

There are no Codex limits for abamectin (defined by Codex as the sum of avermectin B_{1a}, avermectin B_{1b}, and the delta 8,9-isomer of avermectin B_{1a}) in apples. There are no Canadian, or Mexican limits established for abamectin and its delta 8,9 isomer. Therefore, no compatibility problems exist.

cc: PP#0G3930; J. Stokes (CBTS); R. Griffin (CBTS); R.F.; Circu
RDI: PErrico:2/1/94:RLoranger:2/1/94
7509C:CBTS:JStokes:js:Rm 803:CM#2:305-7561:2/2/94

INTERNATIONAL RESIDUE LIMIT STATUS

CHEMICAL Abamectin

CODEX NO. 177

CODEX STATUS:

☒ No Codex Proposal
Step 6 or above

Residue(if Step 8): _____

<u>Crop(s)</u>	<u>Limit</u> <u>(mg/kg)</u>
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PROPOSED U.S. TOLERANCES:

Petition No. PP#1G3930

RCB Reviewer J. Stokes

Residue: Avermectin B₁ and
its delta-8,9 isomer

<u>Crop(s)</u>	<u>Limit</u> <u>(mg/kg)</u>
apples	0.02

CANADIAN LIMITS:

☒ No Canadian limit

Residue: _____

<u>Crop(s)</u>	<u>Limit</u> <u>(mg/kg)</u>
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MEXICAN LIMITS:

☒ No Mexican limit

Residue: _____

<u>Crop(s)</u>	<u>Limit</u> <u>(mg/kg)</u>
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NOTES: _____